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Comparative mutability of wild-type isoalleles at the white loci in *Drosophila melanogaster*

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1. INTRODUCTION

Timoféeff-Ressovsky (1932) reported that two phenotypically indistinguishable wild-type stocks of *Drosophila melanogaster*—designated American and Russian—possessed distinguishable wild-type alleles at their white eye colour (*w*) loci. The w^+ alleles of two stocks were found to mutate at significantly different rates following X-irradiation of adult males. Subsequently, Muller (1935) showed that Timoféeff's Russian and American w^+ alleles could be phenotypically separated by virtue of the different phenotypes of triploid females carrying two doses of a *w* mutant and one or the other w^+ allele. As a result of their demonstration of different wild-type alleles at the *c.i.* locus in *D. melanogaster*, Stern & Schaeffer (1943) designated such alleles, which are difficult to distinguish by conventional genetic methods, as isoalleles. Lefevre (1955) has submitted evidence for the occurrence of mutational isoalleles at the yellow (*y*) body colour locus in *D. melanogaster*.

With the demonstration of the pseudoallelic nature of the *w* locus of *D. melanogaster* (Lewis, 1952; Mackendrick & Pontecorvo, 1952; Green, 1959*a*)—with four recombinationally discrete loci indicated—a re-examination of the genetic basis of isoallelism at these loci was undertaken. Evidence has been presented demonstrating that at least two distinctive w^+ isoalleles occur among a number of laboratory-maintained wild-type stocks (Green, 1959*b* and unpublished). Furthermore, it was shown that the isoalleles are localized to the two right members of the four w^+ loci (Green, 1959*b* and unpublished).

These observations demonstrate that Timoféeff's Russian and American stocks are not unique and motivated a restudy of the comparative mutability of the w^+ isoalleles. For a number of reasons such a restudy is indicated. First, with the detailed genetic analysis of the *w* loci now available, induced mutants can be localized to specific *w* loci. Second, since Timoféeff's study, much data on the frequency and kind of spontaneous and X-ray-induced *w* mutants has been accumulated. In both frequency and eye-colour phenotypes of the *w* mutants these data are at variance with those of Timoféeff. These facts will be discussed *in extenso* below. Therefore, experiments designed to obtain answers to these two questions were carried out. What is the comparative X-ray mutability of the two w^+ isoalleles and what is the frequency of mutation among the recombinationally discrete w^+ loci? In brief, the answers to both questions depend upon first inducing a large number of independent mutants, and second determining the recombination relationships of these mutants. While the former task presents no special difficulties, the latter does.

Any analysis of the recombination relationships of a comparatively large group of independently occurring pseudoallelic mutants is, in *Drosophila*, an exceedingly laborious undertaking. Obviously a simpler method of localization is called for. In the case of the *w* loci one is available which permits at least a partial linkage assignment. This is a phenotypic method for the specification of linkage position of *w* mutants and stems from observations first made by Gans (1953) that *w* mutants can be classified into two types on the basis of their interactions with the independent eye-colour mutant zeste (*z*). Some *w* mutants act as dominant suppressors of *z*; others do not. An extension and a more detailed analysis of this observation was made (Green, 1959*a*) wherein the recombination relationships and *z* interactions of thirty-six independent *w* mutants were studied. It was found that, without exception, all mutants suppressing *z* are located in the two right *w* loci, whereas those failing to suppress *z* are located at the two left *w* loci. This invariable correlation is taken to mean that suppression can be used with confidence in localizing *w* mutants to either the left or right pairs of *w* loci, thereby obviating the need for the more time-consuming recombination study. For purposes of this study, a partial linkage assignment suffices, and the *z* interaction was so employed.

2. EXPERIMENTAL

The two wild-type stocks chosen for study are the well-known laboratory stocks Canton-S and Oregon-R which have been shown to possess dissimilar w^+ isoalleles (Green, 1959*b*). Canton and Oregon can be distinguished phenotypically from each other by their separable eye phenotypes when compounded with two *w* mutants in triploid females or when heterozygous for a *w* mutant in diploid females (Muller, 1935; Green, 1959*b*). A genetical analysis of these stocks has shown that, of their four w^+ loci, the phenotypic difference is determined by different wild-type isoalleles localized to the two right w^+ loci (Green, 1959*b*). For simplicity the four w^+ loci of Canton will be designated $+^C+^C$ and of Oregon $+^O+^O$, where the left + represents the two left loci, the right + the two right loci. Four stocks were used in this study: (1) $y^2\,z\,+^C+^C$, (2) $y^2\,z\,+^O+^O$, (3) $sc\,z\,+^C+^O$, and (4) $sc\,z\,+^O+^C$. Stocks (1) and (2) represent Canton and Oregon into which the identical markers y^2 (body colour) and *z* were introduced, while (3) and (4) are composite wild-type stocks into which *sc* (scute bristles) and *z* were introduced and containing w^+ loci half each from Canton and Oregon. The notation $+^C+^O$ means the left w^+ loci came from Canton, the right from Oregon; $+^O+^C$ the converse. The synthesis of the composite wild-type stocks has been described in detail (Green, 1959*b*).

Males $y^2z+^C+^C$ and $y^2z+^O+^O$ were irradiated simultaneously with 5000 r X-rays (90 kV, 3 mA) delivered at a rate of approximately 300 r/minute. X-ray output was checked with each irradiation with a Victoreen dosimeter and was found to vary about 10%. Following irradiation, males were crossed to females homozygous for the recessive sex-linked mutants y^2, w^a (white-apricot), *v* (vermilion eye colour) and *f* (forked bristles) contained within the sc^8 and *dl-49* inversions. Ten males were crossed to 15–20 females in half-pint milk bottles containing the

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standard corn meal–molasses–brewer's yeast–agar medium. After 4 days, all individuals were transferred to fresh media for a second 4-day period, followed by a second transfer for a third 4-day oviposition period, after which the flies were removed and discarded. F_1 females were scored and all individuals showing altered eye colour and bristle phenotypes were progeny tested by crossing to male sibs. Where *sc z* $+^{C}+^{O}$ and *sc z* $+^{O}+^{C}$ males were used, the identical procedure was followed and body-colour mutations were sought as well.

Depending on the outcome of the progeny tests, the presumptive *w* mutants were handled in one of two ways. Where both y^2 w^a *v f* and *w* mutant males carrying either y^2 *z* or *sc z* were found among the F_2 progeny, the latter were crossed to *y ac z ec* females to determine whether the new *w* mutant did or did not suppress *z*. Where only y^2 w^a *v f* males occurred among the F_2, it was concluded that the chromosome carrying the *w* mutant was male lethal. Now male lethality can be due either to the induction of a *w* lethal mutant or deficiency, or in a few cases to the simultaneous occurrence of a viable *w* mutant and a separate, linked lethal mutation. A simple test was used to distinguish between these two possibilities. It has been previously shown (Green, 1959*c*) that *w* mutants and *w* deficiencies when compounded with the *w* mutant spotted-white (*sp-w*) give phenotypically separable individuals. Thus females *w* mutant/*sp-w* produce a complementary eye colour while females *w* deficiency/*sp-w* have a *sp-w* eye phenotype. Therefore each *w* lethal was compounded with *sp-w*, and if the resultant phenotype was *sp-w*, it was concluded that the *w* lethal was localized to the *w* loci, probably as a deficiency. If, on the other hand, a complementary eye phenotype was found, it was assumed that the lethal chromosome carried a *w* mutant plus a linked, independent recessive lethal and required further testing. Each of these male lethal chromosomes was compounded with a wild-type X chromosome and separation of the *w* mutant and linked lethal through crossing over was sought. Such a separation should result in the recovery of *w*-eyed males. A total of twenty-four independent *w* lethals were found in these experiments. Four gave complementary eye phenotypes on testing to *sp-w*. Subsequently, male viable *w* mutants were recovered from each, demonstrating that the lethal was separable from the *w* loci.

Before presenting the experimental results it is germane to consider the question of the nature of mutations at the *w* loci. On the basis of much experience over the last three decades, it is possible to list the following phenotypic effects which are associated with genetic changes at the *w* loci: (1) viable homogeneous eye colour mutations, (2) lethal *w* mutations and (3) mottled or variegated eye-colour mutations. Each of these mutational events is accompanied by genetic changes which are more or less amenable to cytogenetic analysis. Among the viable, homogeneous eye-colour mutants—especially those apparently induced by X-rays—the following types have been described. The bulk of the mutants are 'point' mutational changes, where 'point' mutation means that such mutants freely recombine with their pseudoalleles. A small proportion of these mutants have been associated with gross chromosomal rearrangements. Thus Demerec (in Bridges & Brehme, 1944) reports that among eight X-ray-induced *w* mutants, seven were cytologically normal and

one was associated with a readily detectable X chromosome inversion. Using crossing over between the mutants *sc* and *z* as a criterion, Green (unpublished) found two of fifteen X-ray *w* mutants to be associated with a chromosome rearragement. All the remainder recombined in an orthodox manner with their pseudoalleles just as did *w* mutants of spontaneous origin. While none has yet been demonstrated, it is conceivable that viable *w* mutants associated with a minute chromosome loss, as described by Green (1959 *c*) for certain recombinant exceptions at the *w* loci, could result from X-ray treatment. Such losses, although cytologically not discernable, could be identified by their failure to recombine freely with pseudoalleles.

Among the lethal *w* mutants, two classes of mutants have been described. Some lethals are apparently devoid of a detectable chromosomal alteration while most others are inseparably associated with a chromosomal loss varying from the barely detectable cytologically to gross losses or rearrangements (Valencia & Muller, 1948; Demerec, *vide supra*). The *w* mottled or variegated mutations are, without exception, associated with chromosomal rearrangement in which the w^+ loci are brought into juxtaposition with heterochromatin. It is of relevance here to mention the *sp-w* mutants which genetically behave as 'point' mutations localized to the *w* loci. Because of their phenotype, *sp-w* mutants could conceivably be mistaken for a *w*-mottle if scored solely in males.

On the basis of the available information it is concluded that the great majority of X-ray-induced mutants at the *w* loci are 'point' mutations as defined above.

3. RESULTS

In Table 1 the frequency of *w* mutations recovered among the several irradiation experiments has been compiled. For each irradiated genotype three classes of *w* mutants are listed: *w* mutants, those with a white eye colour; w^x mutants, those with some eye pigment; and *w* lethals, those which are male lethal as described above. In addition, for purposes of comparison, there are included in Table 1 Timoféeff's experiments with the American ($+^A$) and Russian ($+^R$) wild-type isoalleles together with experiments of other investigators who studied the X-ray induction of mutation at *w* loci.

Perusal of the results shows that no difference was found in the overall frequency of *w* mutations induced in the $+^C$ or $+^O$ w^+ loci. These results are therefore strikingly different from those reported by Timoféeff for $+^A$ and $+^R$, where an appreciable difference in rates will be noted. Furthermore, the results reported here for $+^C$ and $+^O$ differ from those of Timoféeff in two more ways. First, the overall mutation rate —considering only male viable mutants—is *ca.* 1/6400 chromosomes in contrast to Timoféeff's report for $+^A$ of 1/1100 and for $+^R$ of 1/1900. The results reported here compare favourably with those of Valencia & Muller (1948), who found for a dose of 5000 r that viable *w* mutants occurred at a frequency of *ca.* 1/8000 chromosomes. Heptner & Demidova (1936) and Glembozky (1936) found essentially identical mutation rates of 1/4000. Lefevre's results are *ca.* 1/6000 while in two separate earlier experiments of the author, rates of *ca.* 1/8000 and 1/6500 were found. As

Table 1. *Comparative frequency of X-ray-induced* w *mutations*

Genotype irradiated ♂♂	Dose, r	Mutations to *w*: *w*	*w*^{x}	♂ lethal	untested	Total chromosomes	Viable mutants/ 5000 r/10^5 chromosomes	Authority
$y^2\ z\ +^O+^O$		11	1	3	2	77,905	15·4	
$y^2\ z\ +^C+^C$	5000	11	2	3	0	77,008	16·9	This study
sc z $+^C+^O$		9	1	5	2	61,603	16·2	
sc z $+^O+^C$		8	2	9	3	72,115	13·9	
Total		39	6	20	7	288,631	15·6	
$+^C+^C$	5000	11		10	10	72,556	15·2	M. M. Green (unpublished)
v f ^{3n} *car*	5000	14		10	1	132,624	10·6	M. M. Green (unpublished)
*v f**	5000	37		31	51	219,850	16·8	G. Lefevre (unpublished)
$+^A$	4800	41	14	—		59,200	92·9	Timoféeff (1932)
$+^R$	4800	19	21	—		75,300	55·1	Timoféeff (1932)
± (?)	4800	25	12	—		48,500	76·3	Timoféeff (1933)
± (?)	5000–6000	43	10	—		106,500	49·8	Timoféeff (1939)
wild-type	4000	20 (25)†	3 (4)	7	22	106,674	27·2	Heptner & Demidova (1936)
wild-type	6000	8 (7)	2	7	18	46,800	19·2	Heptner & Demidova (1936)
wild-type	4000	21 (26)	3 (4)	8	22	109,803	27·3	Glembozky (1936)

* Summation of results where three different *v* and *f* alleles were used.

† Numbers in ( ) are computed for 5000 r.

indicated in Table 1, Timoféeff consistently obtained comparatively high *w* mutation rates. His 1933 results were *ca.* 1/1300 chromosomes, and those of 1939, 1/2000 chromosomes.

It should be noted that presumptive *w* mutants recorded as untested females in Table 1 have not been included in the computation of mutation rates. The proper disposition of these individuals presents a number of difficulties. In one approach it may be assumed that the *w* mutants of untested females are distributed proportionally among the male viable and lethal classes. By such an apportionment higher rates accrue for all the experiments tabulated other than those of Timoféeff. There is good reason to believe that such an apportionment is neither fair nor realistic. Experience shows that many presumptive mutants detected in females turn out, on progeny testing, to be mosaics arising through chromosome elimination. Any group of untested mutants must be corrected for these mosaics, a correction which undoubtedly varies from experiment to experiment.

The data presented here, together with those of Heptner & Demidova (1936) and Glembozky (1936), differ from those of Timoféeff in yet another respect. This is the ratio of pure white-eyed mutants to pigmented mutants. With the exception of his 1939 study, Timoféeff reports the occurrence of many more pigmented *w* mutants than other investigators listed in Table 1. Moreover, the finding that the $+^R$ isoallele mutates as frequently to pigmented mutants as to white is not in keeping with the results listed here for either $+^C$ or $+^O$, nor with the experience of other investigators. It is of interest to note that among the six pigmented mutants listed in Table 1 derived from $+^O$ and $+^C$, five ranged from tinged to apricot-like, one is a spotted-white allele.

Only brief mention need be made at this point of the *z* reaction of the mutants recovered here. The results, listed in Table 2, show that the bulk of the mutants fail

Table 2. *The* zeste *reaction of X-ray-induced* w *mutants*

Source of *w* mutants	Number of *zeste*	
	Suppressors	Non-suppressors
$y^2\ z\ +^O+^O$	2	10
$y^2\ z\ +^C+^C$	2	11
$sc\ z\ +^C+^O$	2	8
$sc\ z\ +^O+^C$	3	7
Total	9	36

to suppress *z*. The ratio of *z* suppressors to non-suppressors is 1:4. These data parallel those reported for spontaneous *w* mutants where, among 24 chosen at random, 6 were *z* suppressors, 18 not (Green, 1959*a*). By using suppression of *z* as a basis it is possible to compare the mutational frequencies of the left and right halves of the $+^C$ and $+^O$ stocks. From the data of Table 2 it can be readily seen that these rates are essentially identical. A total of 4 mutants/149,123 chromosomes (*z* suppressors) were localized to the right $+^C$ loci, 18/138,611 (non-suppressors of *z*) to the left $+^C$

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loci. For the $+^{O}$ loci the respective totals are 5/139,508 for the right loci and 18/150,020 for the left loci.

Since mutations at the *y*, *v* and *f* loci were also recovered, their frequency is given in Table 3. In the case of the lethal mutants at these loci no attempt was made to determine the frequency of those which were, in fact, a viable mutant plus an independent lethal simultaneously induced. Judging from the *w* mutation data and the X-ray dose used, about 15% of the lethal mutants belong to this category. Thus the viable mutant frequencies are almost certainly slightly low.

Table 3. *Comparative frequency of induced mutations at* y, v *and* f *loci*

Genotype irradiated ♂♂	Mutations to *y*			Mutations to *v*			Mutations to *f*			Total chromosomes
	♂ viable	♂ lethal	untested	♂ viable	♂ lethal	untested	♂ viable	♂ lethal	untested	
$y^2\ z\ +^{O}+^{O}$				5	5	29	9	9	3	77,905
$y^2\ z\ +^{C}+^{C}$				4	10	36	3	12	2	77,008
$sc\ z\ +^{C}+^{O}$	2	0	0	5	8	39	6	8	2	61,603
$sc\ z\ +^{O}+^{C}$	5	4	2	8	9	34	7	5	0	72,115
Total	7 (5·2)*	4	2	22 (7·6)*	32	138	25 (8·7)*	34	7	288,631

* Viable mutants/5000 r/10^5 chromosomes.

A few comments on these data are warranted. The frequency of *f* mutants found is compatible with the report of Valencia & Muller (1948), who state that for 5000 r the *f* mutation rate is *ca.* 1/8000 treated chromosomes. Other investigators report somewhat higher rates as follows: both Heptner & Demidova (1936) and Glembozky (1936) *ca.* 1/6000; Timoféeff (1939) *ca.* 1/4000. Among the *f* lethal mutants found, one-half were associated with a concomitant Minute bristle effect suggesting that these lethals are probably small deletions. The frequency of *v* mutants listed here is appreciably greater than the 1/22,000 frequency noted by Valencia & Muller (loc. cit.) for an equivalent X-ray dose. It will be noted that a striking frequency of F_1 *v* females was found in these experiments, most of whom were sterile on progeny testing. No explanation for this high incidence is immediately obvious.

4. DISCUSSION

The first conclusion warranted by these experiments is that, taken as a whole, the w^+ loci of the Canton and Oregon wild-type stocks mutate at essentially identical rates following X-irradiation. Further, the data show that the two right w^+ loci of Canton and Oregon—demonstrably different (Green, 1959*b*)—mutate at identical rates. Finally, their left w^+ loci which thus far have not been phenotypically separated also are mutationally inseparable. The overall *w* mutation rates both as to frequency and phenotypes of mutants reported here are wholly at variance with those reported by Timoféeff (1932) for the $+^{A}$ and $+^{R}$ wild-type stocks. While it is not possible to reconcile completely the sets of contradictory data, some facts merit discussion. It is, of course, possible to explain away the differences by invoking the

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argument that since the wild-type stocks used here were not identical to those of Timoféeff, there is no basis for discussion. Such an argument is insufficient since there is good reason to believe that the w^+ loci of Timoféeff's $+^R$ and $+^A$ stocks are not totally different from those of Canton and Oregon. Precisely those phenotypic criteria which Muller (1935) employed to distinguish the w^+ isoalleles of $+^R$ and $+^A$ were adopted for separating the w^+ isoalleles of $+^C$ and $+^O$ (Green, 1959*b*). On the basis of these criteria, $+^R$ is equivalent to $+^C$, and $+^A$ to $+^O$. While it is recognized that phenotypic criteria alone cannot establish identity among the w^+ isoalleles, they do suggest in the very least that the wild-type stocks studied by Timoféeff are not widely different from those used here. In addition, a study of eight independent wild-type stocks shows that they fall into but two classes insofar as phenotypic criteria allow the identification of the w^+ loci: six are inseparable from Canton, two from Oregon (Green, unpublished). A detailed genetic analysis of two (Crimea and Formosa) shows that they differ at their two right w^+ loci just as do Canton and Oregon. From these considerations the significant differences in mutation rates of Timoféeff's two stocks and the identical rates of the $+^C$ and $+^O$ stocks are difficult to explain. Needless to say, the situation is confounded by the fact that nothing specific can be stated concerning the extensive genotypic difference which might exist among these wild-type stocks at other loci, loci which could significantly influence the mutation rates of the w^+ loci. However, Timoféeff (1932) presented data to show that the mutation rates of $+^R$ and $+^A$ were quite independent of their background genotypes. Conceivably the background genotypes of $+^R$ and $+^A$ could be sufficiently different from that of Canton and Oregon to bring about the differences noted. In this connexion it should be noted that the mutation rates reported here are fully compatible with rates found by other investigators using, in all likelihood, wild-type stocks of diverse origin. While these facts suggest that the different findings of Timoféeff's and here are not wholly inherent in the nature of the wild-type stocks employed, they, unfortunately, do not provide a clear-cut basis for explaining the differences.

Another difference, similarly difficult to explain, is the comparatively high frequency of pigmented *w* mutants observed by Timoféeff and not correspondingly by others. Perhaps this difference can be explained, in part, by the mutation methods employed. Throughout Timoféeff's experiments, males were irradiated, crossed to attached-X females, and sex-linked mutants sought among the F_1 male progeny. In addition to *w* mutants, eye-colour mutants at other X-chromosome loci will be found among the F_1 males. Since some of these non-allelic loci, e.g. garnet and ruby eye colours, mutate at rates equivalent to or greater than *w* (Valencia & Muller, 1948), experimental provisions must be made to distinguish among the several mutating loci; and this may often have been impossible because of death or sterility of mutant males. Unfortunately, no information is given by Timoféeff as to precisely how this contingency was handled. Is it possible that other eye-colour mutants were inadvertently classified as *w* mutants? Other workers invariably recovered *w* mutants in F_1 females, thereby effectively eliminating any bias from recessive sex-linked mutants at other loci.

Recent information on the genetical organization of the *w* loci has a bearing on yet another mutational event described by Timoféeff. He (1933) reports that, following X-irradiation, the mutants w^a and w^{bl} separately mutated to w^e. If by w^e is meant the mutant whose phenotype does not manifest dosage compensation, there is good reason to be dubious of this transmutation.

The facts as now known are these. Both w^a and w^{bl} occupy loci distinctive from those of all dosage non-compensating mutants including w^e. Furthermore, w^a or w^{bl} coupled to the same chromosome with w^e produces a near-white eye phenotype. Therefore the transmutation of w^a or w^{bl} to w^e requires the simultaneous occurrence of two events: the reversal of w^a or w^{bl} and the mutation of w^e. Such coincidences must be rare indeed, and the occurrence of two exceedingly rare.

The second conclusion warranted by the mutation data presented here is that the two halves of the *w* loci mutate at significantly different rates. Based upon the *z* suppression test the comparative frequency of mutations in the left and right halves of the *w* loci in both the $+^C$ and $+^O$ chromosomes was in the ratio of 4:1. This finding has some relevance for our definition and characterization of the gene. From the operational point of view genes can be characterized by their recombinational relationships, by their functional attributes and by their mutational rates. Previously it has been demonstrated that the recombinational separation of the *w* mutants to left and right halves is paralleled precisely by the *z* reaction of the mutants with the *z* suppressors in the right half, the non-suppressors in the left (Green, 1959*a*). These facts were interpreted to mean that the recombinational separation of the *w* mutants coincides with their functional separation. The data reported here show further that the two halves may be distinguished by the mutation operation. The all-important bearing these facts have on the interpretation of pseudoallelism is almost self-evident. Thus the pseudoallelic components of the *w* loci consist of two groups which can be distinguished by all those operational criteria which can be invoked to distinguish one gene from a non-allelic one. On this basis the conclusion follows that the two halves of the *w* loci are distinctive genes, non-allelic by all current operational criteria. The fact that two independent mutants may manifest the phenotypic criterion of allelism is but a first step in assigning allelic relationships. What the numerous instances of pseudoallelism have so clearly demonstrated is that phenotype as a criterion for allelism is wholly presumptive and cannot stand alone.

5. SUMMARY

1. The X-ray mutability of wild-type isoalleles of the *white-eye* loci in *Drosophila melanogaster* has been determined.

2. No difference in the mutability of the isoalleles was found. However, an appreciable difference in mutation rate of the two halves of the *w* loci was found.

3. The bearing of these data on the problems of isoallelism and pseudoallelism are discussed.

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